Kidney Stones

Introduction

Kidney stones (**nephrolithiasis)** or urology-system stones (**urolithiasis)** are the same thing. You may also hear stones referred to as calculi. Regardless of the name, they all refer to the **presence of stones** anywhere in the GU tract—kidney, ureter, or bladder. The common nonmedical vernacular is kidney stone. The common medical vernacular is nephrolithiasis. We'll go between nephrolithiasis and stone in this lesson.

Let's go back to Gen Chem real quick. Solutes are substances dissolved in solution. Below a critical concentration, a solute will remain dissolved in that solution. If the concentration of a solute exceeds that critical concentration, that solute will precipitate out of solution. Think about the unsweetened tea you just accidentally got. You try to add sugar to it, stirring vigorously, but nope, now there's just sugar at the bottom of the glass. There is sugar dissolved in your tea, but you just added too much sugar for it all to be dissolved. So too for kidney stones.

All stones are salts. We're not talking table salt here. We're talking combination-of-ions salts. A positively charged ion meets a negatively charged ion and they pair up. That salt is soluble like your sugar was in the tea. But if there are too many salts or too little water, those salts can precipitate out of solution. When salts precipitate out of solution they tend to hang out together, forming stones. The primary reason this happens is that the **concentration of the constituents of the stone exceeds the saturation point within the urine**. If you have too much stuff or not enough water, the concentration goes up, and, if the conditions are right, the stuff precipitates out. Stones may be small or large, obstructive or nonobstructive. The presentation is fairly similar for each type of stone (what the patient feels), but the way they are made or the conditions predisposing them are quite unique and make for great test questions.

We review stone presentation, diagnosis, and treatment, then engage the specific types of stones.

General Presentation of Stones

Kidney stones tend to form in the renal pelvis and get stuck in the ureter. Kidney stones are therefore sharp rocks within a hollow tube (ureter). A stone can be **large and obstructive** (nothing can get through and it won't move) or **small and nonobstructive** (it takes a while to get it out, and it shreds up the tube on its way out). Really small stones can just pass without the patient noticing. Larger stones can get stuck. These stones patients feel. **Obstruction** of a hollow viscous **will hurt** whenever a **peristaltic contraction** reaches the obstruction. Since peristalsis is noncontinuous, pain worsens as peristalsis reaches the obstruction, and dissipates as it travels past the stone. This means that kidney stones present with **colicky pain** (comes and goes). Because the kidney is a visceral organ in the retroperitoneal space, there is colicky **flank** pain. Because the embryologic origin of the ureter is in the pelvis, and the ureter is connected to the bladder, that colicky flank pain **will radiate to the groin**. Because stones are sharp, even those that are passing spontaneously can damage the epithelium of the ureter. This will cause bleeding. Most kidney stones present with **hematuria.** The presence of gross hematuria helps, but microscopic blood may be found in the absence of overt hematuria; both count.

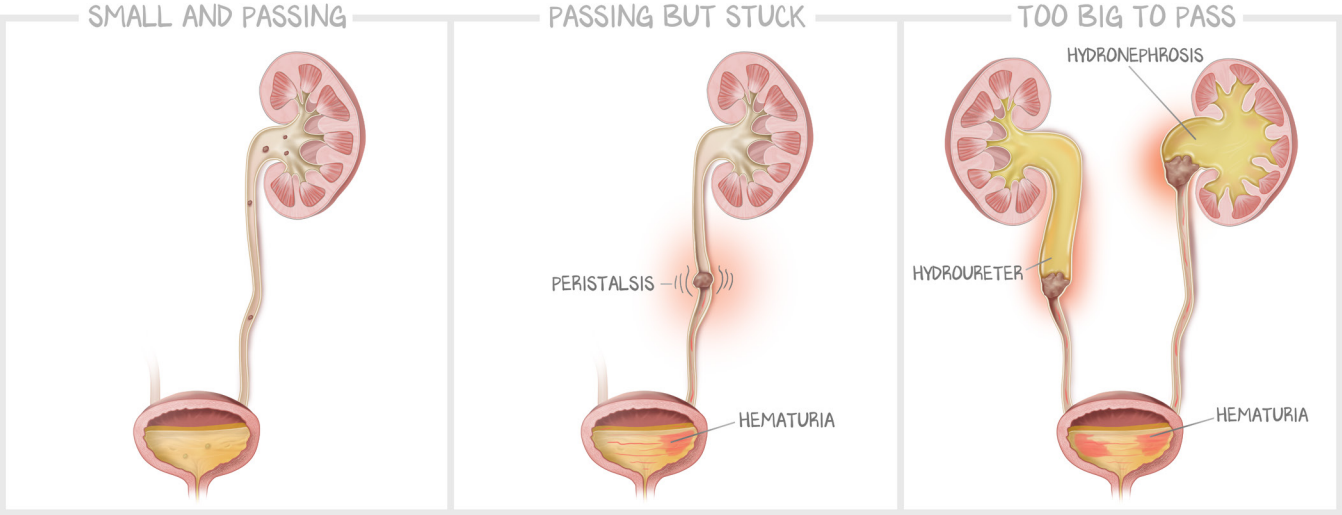


Figure 6.1: Size of Stone to Presentation of Stone
Stones may form and be so small the patient doesn't notice. Symptomatic stones are small enough to pass, but large enough to require peristalsis to propel them through the system. Their sharp edges drag along the ureter wall, causing pain and hematuria. Some stones are too large to pass, resulting in obstruction, leading to hydroureter and hydronephrosis.

Therefore, kidney stones classically present with **colicky flank pain** that **radiates to the groin** and **hematuria**. This is a **painful hematuria** without dysmorphic red blood cells. Painless hematuria could be glomerular disease (casts and dysmorphic RBCs) or malignancy (regular red blood cells).

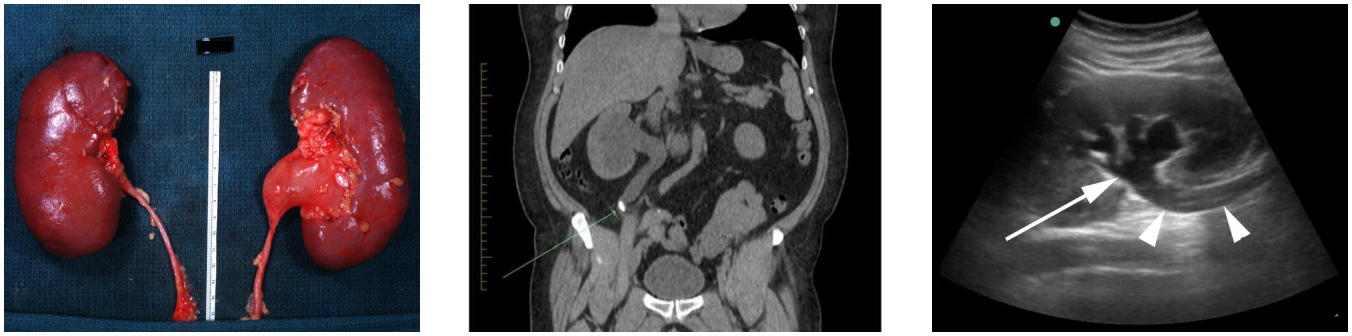
Depending on the size of the stone, there could be evidence of **hydro**. "Hydro" means **hydroureter** (dilation of the ureter proximal to the stone) or **hydronephrosis** (dilation of the kidney itself). Hydro hurts, and so a patient can also present with **costovertebral angle tenderness**. Finally, a complete obstruction can cause **stagnation** of urinary flow, which results in **pyelonephritis**.

Diagnostic Tests in Kidney Stones

A **sensitive** test is **urinalysis**. While there may be a stone that causes no symptoms and therefore has no blood in the urine, a symptomatic stone almost always has some degree of hematuria. The absence of red blood cells in a urine sample means that there is no stone causing a problem.

X-ray is **always wrong**. X-rays were formerly the screening tool for nephrolithiasis before CT scans were cheap and widely available. The problem was that many stones went missed by the X-ray, and providers, having a negative radiographic test, inappropriately ruled out a kidney stone. Some stones are **radiolucent** and will not appear on X-ray, and some **radio-opaque** stones were too small and were missed. Nowadays, **noncontrasted CT of the abdomen** is the gold standard. It can detect radio-opaque stones and also see **hydroureter** and **hydronephrosis**. The study must be **noncontrasted** in order to visualize the stone. Radiocontrast appears bright white. Stones appear bright white. Radiocontrast is cleared in the urine. The radiologist would be unable to see the stone if the contrast got stuck at the level of the stone.

An alternative, in young or pregnant patients where the radiation burden is not worth the benefit of a diagnosis, is to look for dilation of the ureter or kidneys ("hydro") using **renal ultrasound**. While the ultrasound cannot see the stone itself, it can see the dilation proximal to the stone. In the setting of classic symptoms and hematuria, the finding of hydro is enough to make the diagnosis.



(a) (b) (c)

Figure 6.2: Radiographic Presentation of Obstructing Stones
(a) Gross anatomy showing a normal kidney partially crossed polarizers (left) and a kidney with hydroureter (pelvis distended) and hydronephrosis (kidney distended). (b) Coronal CT of the abdomen demonstrating the radioopaque stone (arrow) and the dilated ureters behind it. (c) Ultraound showing a dilated pelvis (arrow) and dilated ureter (arrowheads).

The best test, and the only one that will determine the composition of the stone, is **urine filtration**. The patient urinates through a sieve, letting urine pass into the toilet and trapping any stones. The patient collects these little rocks and turns them over to the lab to determine their composition. This doesn't aid in the diagnosis of the patient's flank pain and hematuria for which they presented. But after the diagnosis is made clinically, after treatment for the acute stone is started, the definitive test is to analyze the stone directly.

Treatment

The treatment of stones is dependent on their size. **Small stones** (< 6 mm) can be passed spontaneously and require only **hydration** (to increase urinary flow to expedite expulsion) and **analgesia**. Slightly larger stones (< 1 cm) may require the addition of **medical expulsive therapy** (tamsulosin and amlodipine), which dilates the ureters and lets stones pass spontaneously. If larger than a centimeter, some decisions need to be made. If the stone is **> 1 cm and proximal** (near the pelvis), then **lithotripsy** (pummeling by ultrasound waves) breaks up the large stone and allows small fragments to pass. If stones are **> 1 cm and distal** (near the bladder) then **endoscopic retrieval** (cystoscopy) can pull them out. If they are really big (like struvite stones), **surgery** may be required.

SIZE	TREATMENT
< 6 mm	Fluids and pain control
< 10 mm	Fluids and pain control And medical expulsive therapy
> 10 mm and proximal	Lithotripsy
> 10 mm and distal	Cystoscopy
Really big?	Surgery

Table 6.1: Stone Treatment by Size

Calcium Oxalate Stones

Calcium binds with oxalate. In the urine, under physiologic conditions, calcium binding to oxalate ensures oxalate's elimination in the urine. We usually want calcium to bind with oxalate. The salt formed by Ca^{2+} and oxalate (which is negatively charged, "oxalate$^-$") is soluble in water at normal concentrations. Salts precipitate into stones (come out of solution) when the concentration of the salts gets too high. That happens when there is too much calcium, too much oxalate, or not enough water. Since we are talking about kidney stones, let's say that again with more clarity. This salt, calcium oxalate, will precipitate into a kidney stone when the concentration of this salt gets too high. That happens when there is too much calcium in the urine, too much oxalate in the urine, or not enough water in the urine. "In the urine" should help to demystify a problem that many students have with calcium oxalate stone formation. We are going to discuss calcium and oxalate as they relate to three compartments—the gut, the blood, and the urine. Just keep in mind that what we care about from the perspective of kidney stones is how much of each substrate is in the urine.

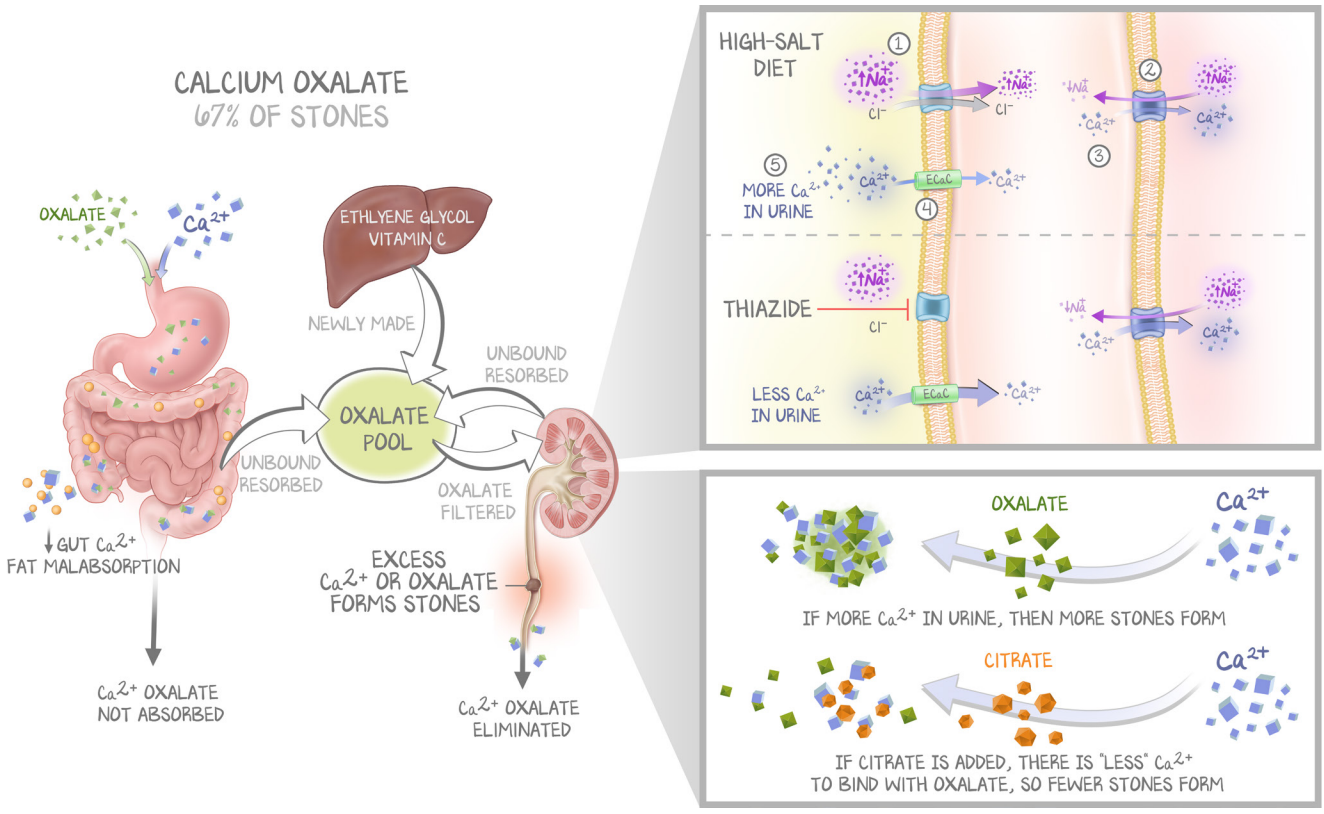


Figure 6.3: Oxalate Metabolism
Yes, this looks tremendously complicated. Look at it first. See the takeaways. Even if you don't understand it or are intimidated by it, engage this figure for a few minutes. Then, after reading the next several pages, come back to this image and work through it again. This LOOKS complicated, but is really quite simple.

Oxalate and calcium are **ingested in the diet**. They exist together in the gut lumen. **Calcium binds to oxalate.** In the gut, the binding of calcium to oxalate prevents the absorption of oxalate. If calcium and oxalate are ingested together, oxalate is not absorbed. This is different than eliminated (from inside the blood to outside the body). See the gut as a way oxalate gets into the blood only and not as a mechanism for elimination. **Oxalate not bound to calcium is absorbed in the colon.** Oxalate absorbed into the colon gets into the blood. Since we are not going to focus on oxalate metabolism or what it does in the body, we are going to term the oxalate-in-the-blood as a nebulous "oxalate pool." Ingesting

excess oxalate in the diet or reducing ingested calcium causes more oxalate to be absorbed by the colon, increasing the oxalate pool. The only way oxalate leaves the body, the only way the oxalate pool decreases, is **elimination in the urine**. To be eliminated in the urine, calcium must bind to oxalate. This similarity, calcium needing to be bound to oxalate in both the colon and the urine, confuses learners. Urinary calcium oxalate is eliminated; fecal calcium oxalate is not absorbed.

Oxalate is also **made by the liver**. "Made by the liver" is a simple way of saying, "the metabolites of certain ingested compounds' hepatic biotransformation result in the formation of oxalate." Oxalate is a byproduct of the metabolism of **vitamin C** and **ethylene glycol**. These things are ingested (vitamin C is okay to ingest in normal amounts; ethylene glycol should never be ingested), absorbed as they are ingested, then are turned into oxalate once in the blood. This increases the oxalate pool.

Any increase in the oxalate pool increases the oxalate in the urine, increasing the risk for calcium oxalate stone formation.

So how does a human INCREASE the oxalate pool from OXALATE SOURCES? By ingesting foods rich in oxalate (nuts, beans), by ingesting excess vitamin C, or by ingesting ethylene glycol.

That was a funny way of asking that last question. That question was asked that way because there are ways for a human to INCREASE the oxalate pool from CALCIUM SOURCES. **Calcium binds oxalate** in the gut. Calcium oxalate is not absorbed. If there were less calcium to bind oxalate in the gut, more of the oxalate would go unbound and get absorbed, increasing the oxalate pool. Ingesting less calcium is technically one way to reduce calcium in the gut. However, calcium is abundant in food supplies, and is really hard not to ingest. Instead, all the ingested calcium could **bind something else**. Calcium does bind to oxalate. But calcium binds to fatty acids much more readily than it does to oxalate. Which means that if there were excess fatty acids in the colon, calcium would not bind to oxalate, and oxalate could be absorbed. Excess fatty acids in the colon occur in **fat malabsorption**. Fat malabsorption occurs with pancreatic insufficiency (chronic pancreatitis, cystic fibrosis), inflammation or loss of the terminal ileum (Crohn's disease), fatty acid resins (ezetimibe), etc.

That was a lot to know about calcium and oxalate absorption. But wait, there's more. Because the thing we care about is the oxalate and calcium concentrations in the urine, all this gut business has done is show us how the oxalate pool would rise. If the oxalate pool increases, more oxalate will be in the urine, the kidney attempting to eliminate the oxalate. But to form stones, there needs to also be excess calcium in the urine.

Calcium regulation is very complicated and is discussed in Endocrine: Parathyroid #2: *The Unhealthy Parathyroid-Calcium Disorders*. We want to stay hyperfocused on the kidney and not overall calcium metabolism. Zero in on the **distal convoluted tubule** (DCT). In Kidney #3: *Glomerular Filtration*, we discussed the Na-Cl cotransporter, the Na-Ca antiporter, and the power of concentration gradients. When there was more sodium chloride absorbed into the cells of the DCT, it made for a less favorable concentration gradient for the sodium-calcium antiporter, an enzyme that resorbs calcium. When we blocked that sodium chloride transporter with a thiazide diuretic, we made the concentration gradient more favorable for calcium resorption. High-salt diets (this time we're talking table salt) cause more NaCl to be ingested, more NaCl to be in the blood, more NaCl to be filtered into the urine, and more NaCl to be resorbed in the DCT, which would weaken the concentration gradient needed for calcium resorption. **High-salt (NaCl) diets increase urinary calcium concentrations** and predispose to calcium oxalate stone formation. **Thiazide diuretics reduce urinary calcium concentrations** and reduce the risk of calcium oxalate stone formation.

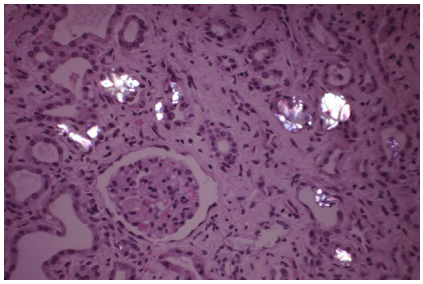
Finally, **citric acid binds calcium** in the urine. If there isn't enough citrate to bind the calcium, more calcium will be free to bind oxalate. While low levels of citric acid are rare to find, it presents a possible treatment intervention for calcium oxalate stones. **Eating more citrate** (citrus fruits) **prevents calcium oxalate stones**.

This isn't an exhaustive list of the mechanisms that increase the urinary calcium concentration or urinary oxalate concentration. But it is the setup for the dietary and lifestyle changes used to address calcium oxalate stones.

PROBLEM	CAUSES	TREATED WITH
Nuts, beans	Increased dietary oxalate	Eat less of those things
Supratherapeutic vitamin C	Increased oxalate formation	Eat less vitamin C
Ethylene glycol	Increased oxalate formation	Don't drink antifreeze
High-salt diet	Reduced urinary calcium resorption	Eat less salt
Low-citrate diet	Increased urinary calcium	Eat citrus fruits
Fat malabsorption	Increased oxalate formation	See GI
Concentrated urine	Increased oxalate and calcium	Drink water

Table 6.2: Dietary Treatment of Oxalate Stones

Why did we spend so much time on oxalate and calcium? Because **calcium oxalate stones are the most common cause of nephrolithiasis** (80% of stones). And look at the interventions. Eat better and drink water. Even if there is a pathologic process that contributes to an increased risk in any one patient, the diet and lifestyle recommendations are the same, and can act to counterbalance that pathologic process. For everyone else without some underlying condition that makes them a higher risk for calcium oxalate stones, eating better in general helps prevent calcium oxalate stones in the first place.



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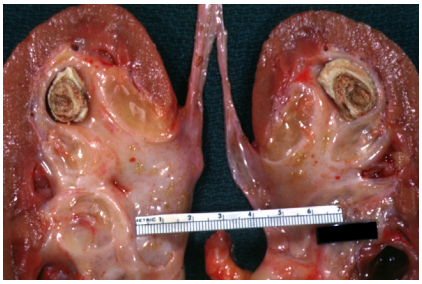

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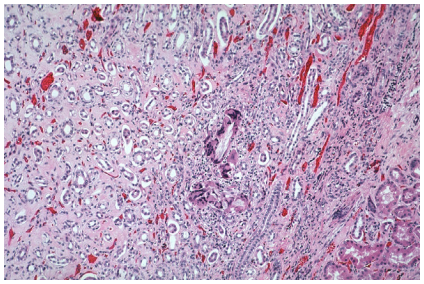

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Figure 6.4: Radiographic Presentation of Obstructing Stones
(a) Calcium oxalate crystals. (b) Staghorn; sliced open kidney with both slices in photo showing sectioned laminated calculus. (c) Uric acid deposit. Low-magnification H&E staining showing nice crystals in the medulla with a giant cell.

Struvite aka Staghorn aka Magnesium Ammonium Phosphate

Struvite stones (5%–10%) tend to form in an **alkaline environment**. The urine is usually acidic. But in the presence of **urea-splitting bacteria** like Proteus, the urine can become alkaline. Therefore patients with **frequent UTIs** are at the highest risk. The struvite stone is also called **staghorn** calculus because of its appearance. These stones are so large that they can consume all of the space available in the calyces and pelvis, forming a **contiguous** structure that resembles the **horns of a stag**. The actual composition of these stones is the combination of magnesium, ammonium, and phosphate, which gives them the

additional name of "triple stones." These are the other **radio-opaque stones**. The mechanism of *Proteus*'s urease causing an increased concentration of the constituents was discussed in detail in Microbiology Bacteria #9: *GNR That Cause Diarrhea*.

Uric Acid Stones

The nucleic acids that are purines are metabolized to uric acid. Purine metabolism, uric acid levels, and the formation of uric acid crystals is the pathogenesis of gout, discussed in Musculoskeletal: Rheumatology #1: *Monoarticular Arthropathy*

For this lesson, we want you to engage uric acid at a high level only, without the details. Uric acid stones (5–10% of all stones) form when uric acid levels are high. Uric acid levels can be high because of increased dietary intake of purine-rich foods (shellfish, beef, seafood, beer), reduced excretion of uric acid in the urine, or because of cancers with high turnover, such as leukemia. High uric acid levels in the blood can precipitate a gouty attack. But high uric acid levels in the blood do not necessarily correlate to high uric acid levels in the urine. Only the conditions of uric acid overproduction (cancers and purine-rich foods) will provoke the formation of uric acid stones. Underexcretion of uric acid causes high blood levels of uric acid, but by definition means less in the urine.

Patients with **gout** or with **hyperuricemia** are at risk of forming uric acid stones. Avoidance of food rich in purines both prevents gout attacks and uric acid stone formation. Treatment with xanthine-oxidase inhibitors such as allopurinol (which reduces the amount of uric acid made by the body) treats gout and uric acid stones. Patients with **leukemia** are also at risk for forming uric acid stones. This risk is highest during treatment—the death of many cells with nuclei at once increases the burden of purine metabolism, producing excess uric acid. This can result in **tumor lysis syndrome**, in which one of the symptoms is renal failure from uric acid stones.

Specific Stones and Risk: Cystine Stones

These stones are **extraordinarily rare** and are a product of **cystine in the urine**. This state occurs only in a rare genetic disorder called **cystinuria** (literally, the disease name is the condition for stones to form). They are **radiolucent**. Be aware that this fourth type exists, but there is nothing you can do to change the risk, and only the rare genetic conditions can ever cause it. The other stones are managed by not-rare diseases or are manageable by diet. Pay attention to those. However, on your board examinations, you must be aware of these stones. Because it is caused by an inheritable disorder, kidney stones **in children** (who rarely develop kidney stones) should make you leap to cystinuria. Cystinuria is caused by a defect of a **transporter in the PCT** which results in the spilling of cystine, ornithine, lysine, and arginine (COLA) into the urine. The diagnosis is made using a **sodium nitroprusside test**. These can also form staghorn calculi.

	CRYSTAL SHAPE		ASSOCIATIONS	X-RAY FINDINGS	CT FINDINGS
Calcium Oxalate	"Envelope" "Dumbbell"		• Ethylene glycol • GI malabsorption diseases	Radiopaque	Radiopaque
Calcium Phosphate	"wedge shaped" "prism"			Radiopaque	Radiopaque
"Struvite"/ Ammonium Magnesium Phosphate	"coffin lid"		• Urease positive bugs • Staghorn calculi	Radiopaque	Radiopaque
Uric Acid	"rhomboid" "rosettes"		• Gout • Leukemia • Tumor lysis syndrome	Radiolucent (U in both lucent and Uric acid)	Minimally visible
Cystine	Hexagonal Remember as "six-tine" instead of cystine since it has 6 sides		• Childhood stones • Staghorn calculi • Ornithine, lysine, and arginine in urine	Radiolucent	Sometimes visible

Table 6.3: Visualizing and Reviewing Kidney Stones

PATIENT	TESTING	TREATMENT
Colicky flank pain that **radiates** to the **groin**, with **hematuria** May present with pyelo, CVA tenderness, renal failure	Urinalysis shows **hematuria** **Noncontrasted CT** is best radiographic test • can visualize radio-opaque stones • can see hydro **Renal ultrasound** if contraindication to CT • can**not** visualize any stone • can see hydro **Urine straining** is the best test	< 0.5 cm—**Analgesia** and **hydration** < 1.0 cm—**Medical expulsive therapy** (CCB, α-blockers) > 1.0 cm and proximal: **lithotripsy** > 1.0 cm and distal: **cystoscopy** > 3.0 cm: **surgery**

Table 6.4: Diagnosis and Management of Kidney Stones